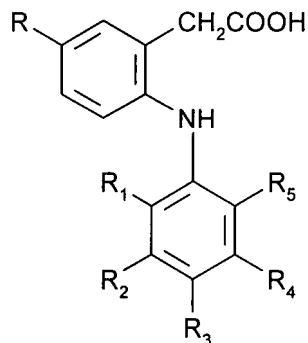


What is claimed is:

1. A compound of formula I



(I)

wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

or a pharmaceutically acceptable salt thereof;

or a pharmaceutically acceptable prodrug ester thereof.

2. A compound according to claim 1 wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is hydrogen; and R_5 is chloro, fluoro or methyl; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

3. A compound according to claim 1 wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

4. A compound according to claim 1 wherein R is methyl or ethyl; R₁ is fluoro; R₂ is fluoro; R₃ is hydrogen, ethoxy or hydroxy; R₄ is fluoro; and R₅ is fluoro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

5. A compound according to claim 1 wherein R is methyl; R₁ is fluoro; R₂ is hydrogen; R₃ is hydrogen or fluoro; R₄ is hydrogen; and R₅ is chloro; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

6. A compound according to claim 1 which is 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid wherein in formula I R is methyl; R₁ is fluoro; R₂ is hydrogen; R₃ is hydrogen; R₄ is hydrogen; and R₅ is chloro; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1 which is 5-methyl-2-(2',4'-difluoro-6'-chloroanilino)phenylacetic acid wherein in formula I R is methyl; R₁ is fluoro; R₂ is hydrogen; R₃ is fluoro; R₄ is hydrogen; and R₅ is chloro; or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1 which is 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetic acid wherein in formula I R is ethyl; R₁ is fluoro; R₂ is fluoro; R₃ is hydrogen; R₄ is fluoro; and R₅ is fluoro; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 which is 5-ethyl-2-(2',4'-dichloro-6'-methylanilino)phenylacetic acid wherein in formula I R is ethyl; R₁ is chloro; R₂ is hydrogen; R₃ is chloro; R₄ is hydrogen; and R₅ is methyl; or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising an effective cyclooxygenase-2 inhibiting amount of a compound of claim 1 which is substantially free of cyclooxygenase-1 inhibiting activity in combination with one or more pharmaceutically acceptable carriers.

11. A pharmaceutical composition comprising an effective cyclooxygenase-2 inhibiting amount of a compound of claim 6 which is substantially free of cyclooxygenase-1 inhibiting activity in combination with one or more pharmaceutically acceptable carriers.

12. A pharmaceutical composition comprising an effective cyclooxygenase-2 inhibiting amount of a compound of claim 7 which is substantially free of cyclooxygenase-1 inhibiting activity in combination with one or more pharmaceutically acceptable carriers.

13. A pharmaceutical composition comprising an effective cyclooxygenase-2 inhibiting amount of a compound of claim 8 which is substantially free of cyclooxygenase-1 inhibiting activity in combination with one or more pharmaceutically acceptable carriers.

14. A pharmaceutical composition comprising an effective cyclooxygenase-2 inhibiting amount of a compound of claim 9 which is substantially free of cyclooxygenase-1 inhibiting activity in combination with one or more pharmaceutically acceptable carriers.

15. A method of treating cyclooxygenase-2 dependent disorders in mammals while substantially eliminating undesirable side effects associated with cyclooxygenase-1 inhibiting activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of claim 1 which is substantially free of cyclooxygenase-1 inhibiting activity.

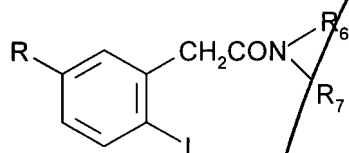
16. A method of selectively inhibiting cyclooxygenase-2 activity in a mammal without substantially inhibiting cyclooxygenase-1 activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of claim 1 which is substantially free of cyclooxygenase-1 inhibiting activity.

17. A method of treating rheumatoid arthritis, osteoarthritis, pain, inflammation in mammals which comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of claim 1 which is substantially free of gastrointestinal ulceration.

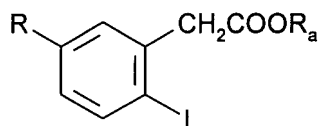
18. A method of treating ocular inflammatory disorders, glaucoma or dry eye disease in mammals which comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of claim 1.

19. A method for the preparation of a compound of formula I according to claim 1 which comprises:

(a) coupling a compound of formula II or IIa



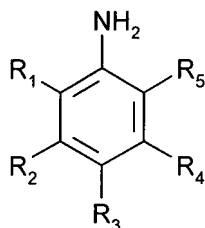
(II)



(IIa)

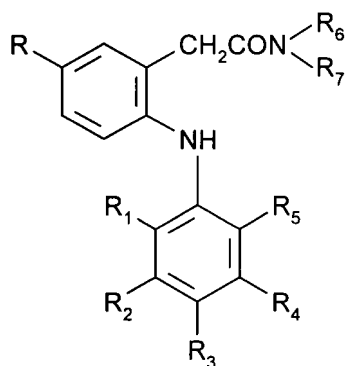
wherein R has meaning as defined; *in claim 1* R_a is lower alkyl; and R₆ and R₇ represent lower alkyl; or R₆ and R₇ together with the nitrogen atom represent piperidino, pyrrolidino or morpholino;

with a compound of formula III

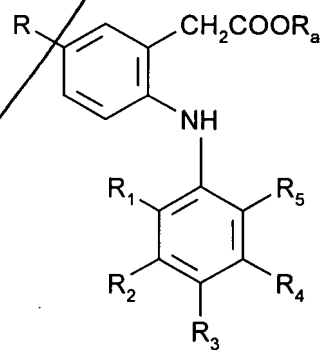


(III)

wherein R₁, R₂, R₃, R₄ and R₅ have meaning as defined in said claim 1, in the presence of copper and cuprous iodide, to obtain a compound of formula IV or IVa



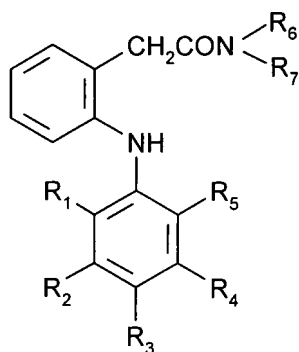
(IV)



(IVa)

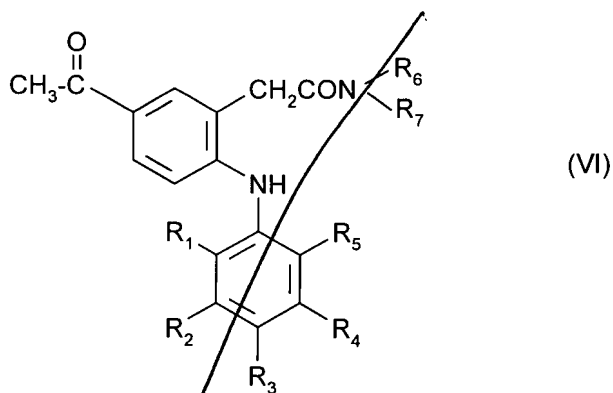
and hydrolyzing the resulting compound of formula IV or IVa to a compound of formula I; or

(b) for compounds in which R represents ethyl, condensing a compound of formula V



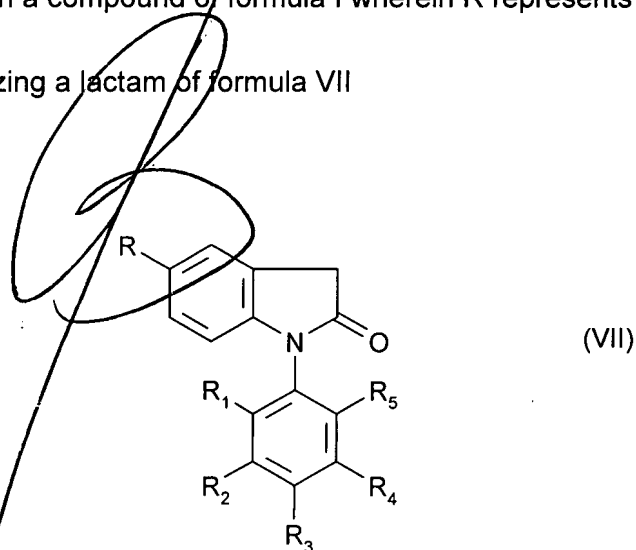
(V)

wherein R_1 - R_5 have meaning as defined above, with a reactive functional derivative of acetic acid, such as acetyl chloride, in a Friedel-Crafts acylation reaction to obtain a compound of the formula VI



wherein R_1 - R_7 have meaning as defined above, and which is in turn hydrogenolyzed and then hydrolyzed to obtain a compound of formula I wherein R represents ethyl; or

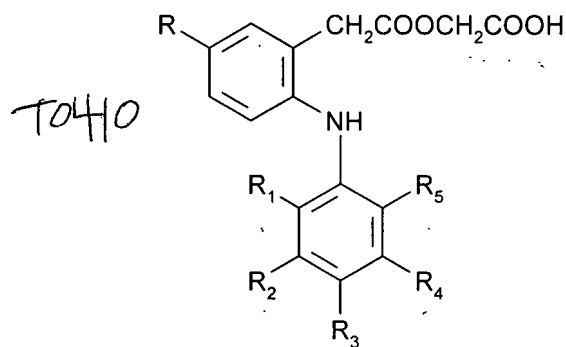
(c) hydrolyzing a lactam of formula VII



wherein R and R_1 - R_5 have meaning as defined, with a strong base; and

in above processes, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting any resulting compound into another compound of the invention; and/or if desired converting a free carboxylic acid of the invention into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting a resulting free acid into a salt or a resulting salt into the free acid or into another salt.

20. A compound according to claim 1 of formula



wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 20 wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is hydrogen; and R_5 is chloro, fluoro or methyl; or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 20 wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; or a pharmaceutically acceptable salt thereof.

23. A compound according to claim 20 wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen, ethoxy or hydroxy; R_4 is fluoro; and R_5 is fluoro; or a pharmaceutically acceptable salt thereof.

5
24. A compound according to claim 20 wherein R is methyl or ethyl; R₁ is fluoro; R₂ is hydrogen; R₃ is hydrogen or fluoro; R₄ is hydrogen; and R₅ is chloro; or a pharmaceutically acceptable salt thereof.

6
25. A compound according to claim 20 which is carboxymethyl 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetate wherein in formula I R is methyl; R₁ is fluoro; R₂ is hydrogen; R₃ is hydrogen; R₄ is hydrogen; and R₅ is chloro; or a pharmaceutically acceptable salt thereof.

7
26. A compound according to claim 20 which is carboxymethyl 5-methyl-2-(2',4'-difluoro-6'-chloroanilino)phenylacetate wherein in formula I R is methyl; R₁ is fluoro; R₂ is hydrogen; R₃ is fluoro; R₄ is hydrogen; and R₅ is chloro; or a pharmaceutically acceptable salt thereof.

8
27. A compound according to claim 20 which is carboxymethyl 5-ethyl-2-(2',3',5',6'-tetrafluoroanilino)phenylacetate wherein in formula I R is ethyl; R₁ is fluoro; R₂ is fluoro; R₃ is hydrogen; R₄ is fluoro; and R₅ is fluoro; or a pharmaceutically acceptable salt thereof.

9
28. A compound according to claim 20 which is carboxymethyl 5-ethyl-2-(2',4'-dichloro-6'-methylanilino)phenylacetate wherein in formula I R is ethyl; R₁ is chloro; R₂ is hydrogen; R₃ is chloro; R₄ is hydrogen; and R₅ is methyl; or a pharmaceutically acceptable salt thereof.

10
29. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 20 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

11
30. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 25 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

12
31. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 26 which is essentially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

13
32. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 27 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

14
33. A pharmaceutical composition comprising an effective antiinflammatory amount of a compound of claim 28 which is substantially free of gastrointestinal ulceration in combination with one or more pharmaceutically acceptable carriers.

15
34. A method of treating cyclooxygenase dependent disorders in mammals without causing undesirable gastrointestinal side effects which comprises administering to a mammal in need thereof an effective amount of a compound according to claim 29 which is substantially free of gastrointestinal ulceration.

16
35. A method of treating rheumatoid arthritis, osteoarthritis, pain or inflammation in mammals without causing undesirable gastrointestinal side effects which comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of claim 30 which is substantially free of gastrointestinal ulceration.

add as
add
C1